REMARKS

Claims 2-12, 17 and 31-43 were pending in the application. Claims 2-7, 9, 10, 12, 17 and 38-40 have been amended, and new claims 44-50 have been added. Support fore the amendments can be found in the specification and claims as originally filed.

In compliance with 37 C.F. R. §1.121, a marked up version entitled "Version with Markings to Show Changes Made," is attached hereto as Appendix I. In addition, for the Examiner's convenience, a clean copy of all the pending claims is set forth in Appendix II.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election/Restriction

The Restriction Requirement and Election of Species set forth in Paper No. 8, has been deemed proper and rendered final on the ground that "the first claim does not provide a technical feature that is distinguished over the prior art, as evidenced by WO 94/09135, which discloses that inhibitors of p21 can be introduced into cells and interfere with p21 binding to complex members" (Paper No. 12, page 2).

Applicants maintain that the requirement is improper and request reconsideration and withdrawal thereof for the following reasons. As in the corresponding PCT case, the currently pending claims are all based on Applicants discovery of the regions and fragments of p21 that bind to Cdk4 and cyclin D1. These regions and fragments of p21 constitute a novel technical feature that links all of the pending claims together to form a single general inventive concept as required by Rule 13.1.

Indeed, in the International Preliminary Examination Report, the presently claimed subject matter was deemed to meet the requirements of novelty, inventive step and industrial applicability under PCT Article 33. The Examining Authority found that,

> "Assays to identify compounds affecting the interaction of p21 with cyclinD1 and/or Cdk4 by using fragments of p21 have not been disclosed in the prior art...The various uses of p21 fragments have also not been disclosed in the prior art."

And further,

> [The prior art] is silent with respect to domains important for interaction with cyclin D1 and Cdk4. This information cannot be derived from the prior art in an obvious manner. Therefore, also the use of such domains (or fragments) in methods according to [the] claims ... cannot be derived from the prior art" (Form PCT/409 Sheets 2 and 3).

Applicants respectfully submit that the reference cited in the instant Office Action, WO 94/09135 (Beach *et al.*), fails to destroy either the novelty or inventiveness of the presently claimed invention. Beach *et al.* teach the cloning of cyclin D1, and report that this molecule co-precipitates with Cdk4, p21 and PCNA. They further teach that this quaternary complex is involved in cell cycle regulation, and generally propose that agents which prevent complex formation by interfering with any of the constituents of the complex would be useful in modulating cell division. However, the teachings of Beach *et al.* merely invite the skilled artisan to embark on a research program to identify molecules capable of disrupting interactions between constituents of the p21/Cdk4/cyclinD1/PCNA complex. Moreover, Beach *et al.* do not teach the specific domains or fragments of p21 which are required for the interaction with cyclin D1 and Cdk4, nor do they teach the uses of these domains or fragments as presently claimed.

In view of the above, Applicants respectfully submit that all of the pending claims relate to form a single general inventive concept as required under PCT Article 3(4)(iii) and 17(3), PCT Rule 13, and 37 CFR § 1.475. Accordingly, the Restriction Requirement

and Election of Species are improper and should be withdrawn. In the event that the finality of the requirement is maintained, Applicants expressly retain the right to petition the Commissioner to review the requirement as set forth in CFR §1.144.

Claim Objection

Claim 9 was objected to because sequences referred to in the claim were not identified by SEQ ID NO. Claim 9 and all of the pending claims have been amended to include reference to SEQ ID NOs where appropriate, and withdrawal of the objection is respectfully requested.

Claim 2 was objected to on the ground that it is directed to non-elected subject matter. Applicants respectfully submit that claim 2 falls within Group I, the group Applicants previously elected with traverse. With regard to the election of species requirement, Applicants will make the appropriate amendment or cancellation of the claim upon final rejection or allowance of the pending claims. MPEP 809.02(c), 821.01

Rejections Under 35 USC § 112

Claims 2, 6, 8, 10-12 and 17 were rejected as indefinite on the ground that the use of the term "and/or" renders the claimed subject matter unclear. The claims have been amended to remove this term and to more specifically point the claimed subject matter. Accordingly, the rejection has been rendered moot, and withdrawal thereof is requested.

Rejection Under 35 USC § 103

Claims 2, 6, 8, 10-12 and 17 were as unpatentable over WO 94/09135 (Beach *et al.*) in view of Xiong *et al.* (1993), on the ground that,

> Beach *et al.* discloses that inhibitors of p21 can be introduced into cells and interfere with p21 binding to complex members (i.e. including cyclin D) (page 4, lines 27-28). Beach et al. also discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23). Beach discloses

> a method of screening compound for their ability to inhibit or suppress the transformation of a cell, which may include prevention of formation of complexes including cyclin D, p21 and CDK (page 24, line 12 to page 25, line 9). Beach et al. does not list the sequence of p21, hence the Xiong et al. reference is cited to exemplify that the sequence of p21 comprises the claimed KRRLIFSK sequence (Paper 12, pp. 3-4).

Applicants respectfully traverse this rejection. As discussed above, Beach *et al.* teach that the cyclin D1/Cdk4/p21/PCNA quaternary complex is involved in cell cycle regulation, and generally propose that agents which prevent complex formation by interfering with any of the constituents of the complex would be useful in modulating cell division. Beach *et al.* do not provide any guidance whatsoever which would motivate the skilled artisan to focus on p21 over any of the other constituents of the complex. Still less, do Beach *et al.* teach which regions of p21 might be effective in inhibiting complex formation, let alone teach the specific peptides disclosed in the instant application. Indeed, the particular portions of the reference cited in the Office Action are all directed to vague statements regarding the possibility that inhibitors of p21 could be useful in preventing complex formation, which are reiterated with regard to PCNA, cyclin D1 and Cdk4. Such broad, sweeping statements simply represent an invitation to a fishing expedition without any prediction of success.

Xiong *et al.* fails to cure the deficiencies of Beach *et al.* This reference discloses the full-length nucleotide and amino acid sequence of p21. Xiong *et al.* do not teach particular regions or fragments of p21, or suggest that anything less than the intact p21 protein might be useful. Thus, the citation of Xiong *et al.* in support of the instant rejection on the ground that this reference shows that the sequence of p21 comprises the claimed KRRLIFSK sequence is solely based on hindsight reconstruction. In the absence of the teachings of Applicants specification, one skilled in the art presented with the teachings of Beach *et al.* and Xiong *et al.*, could not have predicted that fragments of p21 containing the claimed KRRLIFSK sequence would capable of inhibiting Cdk4 activity,

or that the particular fragments of p21 disclosed by Applicants would be useful in the presently claimed methods.

Accordingly, Applicants respectfully submit that this rejection is improper and should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified Application, the Examiner is invited to call the undersigned at (617) 227-7400.

Date: August 8, 2001

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APPENDIX I

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

2. (Thrice Amended) A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1 ~~and/or Cdk4~~, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

3. (Twice Amended) The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 4 (SEQ ID NO:4).

4. (Thrice Amended) The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence **K**xxRRyFz**P** (SEQ ID NO:14).

5. (Amended) The method according to claim 4 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 2 (SEQ ID NO:2).

6. (Twice Amended) The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence xyLzF.

7. (Amended) The method according to claim 6 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 10 (SEQ ID NO:10).

9. (Amended) The method according to claim 8 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 11 (SEQ ID NO:11).

10. (Twice Amended) The method according to claim 2, 44 or 45 further comprising testing the ability of the compound to modulate a p21- mediated effect on Cdk4 activity.

12. (Twice Amended) A method according to claim ~~1 or 2~~ 10 wherein induction of G1 cell-cycle arrest is tested.

17. (Twice Amended) A method comprising obtaining a compound which modulates the interaction or binding between p21 and cyclin D1 ~~and/or Cdk4 and/or modulates a p21-mediated effect on Cdk4 activity~~ in accordance with claim 2, further comprising formulating the compound into a composition including at least one additional component.

38. (Thrice Amended) A method of interfering with interaction between p21 and cyclin D1 ~~and/or Cdk4~~, comprising contacting p21 ~~and/or~~ Cdk4 or cyclin D1 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.

39. (Thrice Amended) A method of modulating a p2l-mediated effect on Cdk4 activity, the method including contacting p21 ~~and/~~or Cdk4 with a substance which comprises a peptide fragment of p21, or a derivative thereof, which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of a said fragment.

40. (Amended) A method according to claim 38 ~~or claim 39~~ , 39, 48 or 49 which takes place in vitro or ex vivo.

44. (New) A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising Cdk4 or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

45. (New) A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1 and Cdk4, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test

compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

46. (New) A method comprising obtaining a compound which modulates the interaction or binding between p21 and Cdk4 in accordance with claim 44, further comprising formulating the compound into a composition including at least one additional component.

47. (New) A method comprising obtaining a compound which modulates the interaction or binding between p21, cyclin D1 and Cdk4 in accordance with claim 45, further comprising formulating the compound into a composition including at least one additional component.

48. (New) A method of interfering with interaction between p21 and Cdk4, comprising contacting p21 or Cdk4 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);
or a derivative, fragment, analog or functional mimetic of said fragment.

49. (New) A method of interfering with interaction between p21 and cyclin D1 comprising contacting p21 or cyclin D1 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);
or a derivative, fragment, analog or functional mimetic of said fragment.

50. (New) A method of interfering with interaction between p21, cyclin D1 and Cdk4 comprising contacting p21, cyclin D1 or Cdk4 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.

APPENDIX II - Pending Claims

2. A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

3. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 4 (SEQ ID NO:4).

4. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence **K**xxRRyFz**P** (SEQ ID NO:14).

5. The method according to claim 4 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 2 (SEQ ID NO:2).

6. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence xyLzF.

7. The method according to claim 6 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 10 (SEQ ID NO:10).

8. The method according to claim 6 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence KRRLIFSK (SEQ ID NO:23).

9. The method according to claim 8 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 11 (SEQ ID NO:11).

10. The method according to claim 2, 44 or 45 further comprising testing the ability of the compound to modulate a p21- mediated effect on Cdk4 activity.

11. A method according to claim 10 wherein RB phosphorylation is tested.

12. A method according to claim 2, 44 or 45 wherein induction of G1 cell-cycle arrest is tested.

17. A method comprising obtaining a compound which modulates the interaction or binding between p21 and cyclin D1 in accordance with claim 2, further comprising formulating the compound into a composition including at least one additional component.

31. A method of treating a hyperproliferative disorder in a cell which comprises contacting the cell with or causing the cell to express a substance selected from the group consisting of:

(i) a fragment of p21, or an active portion or derivative thereof;

(ii) a peptide fragment including the motif xyLzF, wherein y and z are any amino acid and x derivative of said peptide fragment inhibiting Cdk4;

(iii) a peptide fragment including the motif **K**xxRRyFz**P** (SEQ ID NO:14), wherein x is any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different; and

(iv) a functional mimetic of (i), (ii) or (iii) with the property of inhibiting Cdk4; such that a hyperproliferative disorder is treated.

32. The method of claim 31 wherein the substance comprises or consists essentially of a peptide fragment with a sequence which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

and KRRLIFSK (SEQ ID NO:23),

or a functional mimetic of any of these peptide sequences with the property of inhibiting Cdk4.

33. The method of claim 32 wherein the substance consists essentially of the peptide KRRLIFSK (SEQ ID NO:23) or a functional mimetic thereof which inhibits Cdk4.

34. The method of any of claims 31 to 33 wherein the substance is coupled to a carrier for delivery to cells.

35. The method of claim 34 wherein the substance is a peptide and is coupled to a carrier peptide with the sequence RQIKIWFQNRRMKWKK (SEQ ID NO:15).

36. A method of ameliorating a disorder characterized by abnormal cell proliferation comprising contacting a cell with the peptide KRRLIFSK (SEQ ID NO:23), or a functional mimetic thereof with the property of inhibiting Cdk4 such that abnormal cell proliferation is ameliorated.

37. The method according to claim 36, wherein the disorder is a hyperproliferative disorder.

38. A method of interfering with interaction between p21 and cyclin D1, comprising contacting p21 or cyclin D1 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.

39. A method of modulating a p2l-mediated effect on Cdk4 activity, the method including contacting p21 or Cdk4 with a substance which comprises a peptide fragment of p21, or a derivative thereof, which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of a said fragment.

40. A method according to claim 38, 39, 48 or 49 which takes place in vitro or ex vivo.

41. A method according to claim 39 which takes place in vivo.

42. The method of claim 31 or 32, wherein the cell is contacted with the substance.

43. The method of claim 31 or 32, wherein the cell is caused to express the substance by expression by the cell of a nucleic acid molecule encoding the substance.

44. A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising Cdk4 or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an

inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

45. A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1 and Cdk4, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

46. A method comprising obtaining a compound which modulates the interaction or binding between p21 and Cdk4 in accordance with claim 44, further comprising formulating the compound into a composition including at least one additional component.

47. A method comprising obtaining a compound which modulates the interaction or binding between p21, cyclin D1 and Cdk4 in accordance with claim 45, further comprising formulating the compound into a composition including at least one additional component.

48. A method of interfering with interaction between p21 and Cdk4, comprising contacting p21 or Cdk4 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.

49. A method of interfering with interaction between p21 and cyclin D1 comprising contacting p21 or cyclin D1 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.

50. A method of interfering with interaction between p21, cyclin D1 and Cdk4 comprising contacting p21, cyclin D1 or Cdk4 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different) (SEQ ID NO:14);

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R);

or a derivative, fragment, analog or functional mimetic of said fragment.